Development of Viral Diseases and a Viral Disease-Like Syndrome After Extracorporeal Circulation

By George R. Holswade, M.D., Mary Allen Engle, M.D., S. Frank Redo, M.D., Edward I. Goldsmith, M.D., and Jeremiah A. Barondess, M.D.

The now fairly common use of extracorporeal circulation has resulted in a large group of patients who have been subjected to the hazards of multiple blood transfusions. It is somewhat surprising that a greater incidence of viral diseases has not been noted in the patients who survive those procedures. Kreeel et al. studied 20 patients after successful open-heart surgery utilizing a bubble oxygenator, and described a post-perfusion syndrome which included anemia, leukocytosis, hematuria, albuminuria, and fever. In six of their patients, atypical lymphocytes, similar to those seen in infectious mononucleosis, appeared in the peripheral blood smears, and in one patient splenomegaly and elevation of the heterophile antibody titer subsequently developed. Wheeler et al. reported an unusual syndrome characterized by fever, splenomegaly, and atypical lymphocytes occurring in patients after an open-heart operation in which a rotating disk-type oxygenator was used. This syndrome was seen in 6 of 54 patients who survived open-heart operations during one year, an incidence of 11 per cent. An elevation of the heterophile antibody titer was not found in these patients. The syndrome appeared three to seven weeks after operation, followed a benign course lasting one to three weeks, and required no specific therapy. An infectious viral etiology was suggested.

In the first 170 consecutive patients who survived open-heart operation at The New York Hospital–Cornell Medical Center, a syndrome similar to that described by Kreeel et al. and Wheeler et al. was seen in 14 patients (table 1), an incidence of 8 per cent. In all cases, a rotating disk-type oxygenator was used. In the first half of the series, finger pumps were used; in the second half, roller pumps were used. The syndrome was characterized by malaise, fever, normal or low total white blood counts, lymphocytosis, and, in most cases, splenomegaly and hepatomegaly.

The ages in which this syndrome appeared ranged from 4 to 44 years and followed, in general, the same distribution as for the entire group. There were eight women and six men, but again this follows the slight predominance of women for the group as a whole. In all but one case, the operation was for repair of a congenital cardiac defect, most of which were atrial septal defects. The one case of acquired heart disease was calcific aortic stenosis. This heavy predominance of congenital cardiac disease does not follow the group as a whole, in which 70 per cent were of the congenital type.

It is of interest that most cases of this syndrome occurred in one year: eight in 1959, with only three in 1958, three in 1960, and none in 1961, the last year covered by this report. Approximately the same number of open-heart procedures was performed in each of these four years. The reason for the predominance of cases in 1959 is not apparent.

The time of extracorporeal circulation was under 30 minutes in most cases, and was under one hour in all cases. Perfusion times tended to be longer in cases in which the syndrome was not seen, especially in the repair of acquired valvular defects. Duration of extracorporeal circulation, at least within the usual limits, would not appear to have any relation to this syndrome.

The fever associated with this syndrome was not high, usually ranging between 38 and 39°C. Typically, the onset of fever and associated symptoms and signs was delayed for
Heterophile antibody titers were determined in 10 patients, but there was significant elevation in only one case.

In four patients, splenomegaly was delayed three to seven weeks after operation, whereas the spleen remained palpable in some cases for several months. The enlargement of the spleen was in most cases, of short duration, whereas the spleen remained palpable in some cases for several months.

Table 1

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Date of operation</th>
<th>Perfusion time in minutes</th>
<th>Duration of fever in days</th>
<th>Lymphocytes (peak %)</th>
<th>Virocites</th>
<th>White blood count</th>
<th>Hepatomegaly</th>
<th>Splenomegaly</th>
<th>Heterophile antibody titer</th>
<th>Blood type</th>
<th>Total units of blood used</th>
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<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>M</td>
<td>A-V canal</td>
<td>4/24/58</td>
<td>46</td>
<td>10</td>
<td>82</td>
<td>+</td>
<td>9,600</td>
<td>+</td>
<td>+</td>
<td>1:7</td>
<td>O+</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>F</td>
<td>A.S.D.</td>
<td>6/26/58</td>
<td>21</td>
<td>7</td>
<td>46</td>
<td>+</td>
<td>7,700</td>
<td>+</td>
<td>+</td>
<td>1:14</td>
<td>A+</td>
<td>17</td>
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<tr>
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<td>23</td>
<td>M</td>
<td>A.S.D.</td>
<td>7/8/58</td>
<td>22</td>
<td>30</td>
<td>66</td>
<td>+</td>
<td>7,000</td>
<td>+</td>
<td>+</td>
<td>1:96</td>
<td>O+</td>
<td>19</td>
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<tr>
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<td>5</td>
<td>F</td>
<td>A.S.D.</td>
<td>1/6/59</td>
<td>21</td>
<td>7</td>
<td>65</td>
<td>+</td>
<td>6,900</td>
<td>+</td>
<td>+</td>
<td>1:112</td>
<td>O+</td>
<td>9</td>
</tr>
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<td>F</td>
<td>A.S.D.</td>
<td>3/3/59</td>
<td>17</td>
<td>7</td>
<td>68</td>
<td>+</td>
<td>6,000</td>
<td>+</td>
<td>+</td>
<td>1:77</td>
<td>O+</td>
<td>19</td>
</tr>
<tr>
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<td>7</td>
<td>M</td>
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<td>14</td>
<td>7</td>
<td>41</td>
<td>+</td>
<td>8,500</td>
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<td>+</td>
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<td>O+</td>
<td>9</td>
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<tr>
<td>7</td>
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<td>16</td>
<td>76</td>
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<td>A+</td>
<td>16</td>
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<tr>
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<td>A.S.D.</td>
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<td>52</td>
<td>32</td>
<td>76</td>
<td>+</td>
<td>14,600</td>
<td>+</td>
<td>+</td>
<td>1:77</td>
<td>O+</td>
<td>26</td>
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<td>M</td>
<td>A.S.</td>
<td>9/16/59</td>
<td>27</td>
<td>18</td>
<td>38</td>
<td>+</td>
<td>7,000</td>
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<td>+</td>
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<td>18</td>
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<tr>
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<td>A.S.D.</td>
<td>10/8/59</td>
<td>39</td>
<td>33</td>
<td>59</td>
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<td>33</td>
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<td>A.S.D.</td>
<td>1/7/60</td>
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<td>32</td>
<td>38</td>
<td>+</td>
<td>13,000</td>
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<td>+</td>
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<td>O+</td>
<td>45</td>
</tr>
<tr>
<td>13</td>
<td>19</td>
<td>M</td>
<td>A.S.D.</td>
<td>7/21/60</td>
<td>16</td>
<td>22</td>
<td>64</td>
<td>+</td>
<td>9,500</td>
<td>+</td>
<td>+</td>
<td>1:112</td>
<td>O+</td>
<td>15</td>
</tr>
</tbody>
</table>

A-V canal, atrioventricular canal; A.S.D., atrial septal defect; Valv. P.S., valvular pulmonic stenosis; Anom. P.V., anomalous pulmonary valve; A.S., aortic stenosis; +, positive.
stances of elevation of heterophile titer may have been missed, however, since repeated determinations were not made in several patients.

Case Report

Case number 3, E.A. (NYH 711 749), a 23-year-old white, single, schoolteacher, had had a known cardiac murmur since the age of eight years, but gave no history of rheumatic fever. During the year before her operation, she had tired easily and had noted two-flight dyspnea, two-pillow orthopnea, and occasional pain in the chest. The physical findings, roentgenogram of the chest, and electrocardiogram were compatible with the diagnosis of atrial septal defect, which was confirmed by cardiac catheterization.

On July 8, 1958, an open-heart operation with cardiopulmonary bypass was performed, and a large ostium secundum–type of atrial septal defect was repaired. Her postoperative course was complicated by fever and atrial fibrillation. There was mild icterus, with the total serum bilirubin rising to 5.3 mg. per cent on the second postoperative day. A slow fall in the hematocrit over a two-week period was attributed to a delayed destruction of red blood cells and the bilateral accumulation of pleural fluid. Cultures of serosanguineous fluid from repeated thoracenteses were negative, as were repeated blood cultures. Antibiotics were discontinued on the twelfth postoperative day, but were started again nine days later in view of the continued febrile course.

For a time, she was considered to have the postpericardiotomy syndrome, because of pleural effusions and pleuritic pain in the presence of a low white blood count and a spiking fever. She slowly improved and was afebrile by her thirty-ninth postoperative day. However, the lymphocyte count, which had been normal until this time, rose to 63 per cent and many virocytes were seen on the smear. Both the spleen and liver were palpable and, during the next week, could be easily felt between 4 and 5 cm. below the costal margins. There was moderate cervical lymphadenopathy. The heterophile antibody titer was 1:224, and two days later reached a peak of 1:996. At this time, total serum bilirubin level was 0.6 mg. per cent, total serum protein level was 6.6 Gm. per cent with an A/G ratio of 3.7/2.9, thymol turbidity was 12 units, cephalin flocculation was 22 units, and serum transaminase (SGOT) was 29 units. She gradually improved, but at the time of discharge on the sixthtieth postoperative day, the spleen and liver were still palpable, the peripheral blood smear showed 66 per cent lymphocytes, and the heterophile titer was 1:448, with the guinea pig absorption titer also 1:448.

One month after discharge, the liver and spleen were still palpable and the heterophile titer was 1:224. She gained strength slowly and was not able to return to teaching for a year after her operation. Cardiac catheterization was repeated 15 months after operation and showed no residual shunt. At this time, the lymphocyte count was 44 per cent; the heterophile titer was 1:14. She was completely recovered and felt that her exercise tolerance was greatly increased over that preoperatively.

Comment

Ten of the patients were blood type O Rh positive, three were A Rh positive, and one was B Rh positive. The total number of units of blood used in each case varied from 8 to 45, an average of 17.6 units per case. This includes heparinized blood used to prime the pump oxygenator, and all citrated blood given before, during, and after operation. In the three cases in which the number of units administered had exceeded 25, secondary bleeding had occurred, and reoperation for the control of hemorrhage was necessary. A gradual drop in the hematocrit during the first 10 days postoperatively was seen consistently in all our open-heart cases and was corrected by additional transfusions or iron therapy as indicated. Thus, although a low hematocrit may have occurred temporarily in some of these 14 patients, anemia per se was not considered a characteristic feature of this syndrome.

Homologous serum hepatitis occurred in only one of the 170 survivors. In this case, one of the donors became ill with acute viral hepatitis 18 days after blood donation. The patient was given immune globulin, but developed hepatitis nine weeks after operation. Of interest, but of questionable significance, is the fact that during the last year and a half, two of the operating surgeons for these 170 patients developed acute viral hepatitis, presumably of homologous serum origin.

In our institution, blood for open-heart operations is drawn on the morning of operation from donors in the hospital environment: doctors, nurses, medical students, and other hospital personnel. All donors are carefully screened, yet unrecognized reservoirs of mono-
nucleosis and similar viral diseases may exist in this group.

Summary

In 170 consecutive patients with congenital or acquired cardiac disease who survived open-heart operations, 14 patients (8 per cent) developed a syndrome characterized by malaise, fever, normal or low white blood count, lymphocytosis, and, in most cases, splenomegaly and hepatomegaly. The onset was usually delayed from three to six weeks after operation. Although this syndrome clinically resembled infectious mononucleosis, this diagnosis could be clearly established in only one case by heterophile antibody determinations. Nevertheless, the presence of virocytes and other similarities suggest a viral etiology for the other 13 cases.

References


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